Pharmacokinetics and Clinical Efficacy of Oral Morphine Solution and Controlled-Release Morphine Tablets in Cancer Patients

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Twenty-three adult patients with chronic pain due to cancer completed a double-blind, randomized, two-phase crossover trial comparing plasma morphine concentrations and analgesic efficacy of oral morphine sulfate solution (MSS) and controlled-release morphine sulfate tablets (MS Contin [MSC], Purdue Frederick, Inc., Toronto, Ontario, Canada). MS Contin was given every 12 hours to all patients except those whose daily morphine dose could not be equally divided into two 12-hour doses with the tablet strengths available. MSS was given every 4 hours. Patients received both of the test drugs for at least 5 days, and, on the final day of each phase, peripheral venous blood samples for morphine analysis were obtained. Eighteen patients received MSC every 12 hours, and five received it every 8 hours. The same total daily morphine dose was given in both phases. In the 18 patients who received MSC every 12 hours, the daily morphine dose was 183.9 ± 140.0 mg (mean ± SD). In this group, the mean area under the curve (AUC) with MSC was 443.6 ± 348.4 ng/ml/hour, compared with 406.8 ± 259.7 ng/ml/hour for MSS ($P > 0.20$). Mean maximum morphine concentrations (C_{max}) for MSC and MSS were 67.9 ± 42.1 and 58.8 ± 30.3 ng/ml, respectively ($P > 0.05$). Mean minimum morphine concentrations (C_{min}) were 17.0 ± 17.7 and 18.3 ± 15.0, respectively ($P > 0.30$). There was a significant difference ($P < 0.001$) between the two drugs in time required to reach maximum morphine concentration (T_{max}). Mean T_{max} after MSC occurred at 3.6 ± 2.3 hours. After MSS, it occurred at 1.3 ± 0.4 hours. In the five patients who received MSC every 8 hours, the findings paralleled those in the principal group, with no significant differences between MSC and MSS in C_{max} or C_{min} and a highly significant difference between the two in T_{max}. However, in this small group of patients, the AUC with MSC was significantly ($P = 0.04$) greater than that with MSS. All patients had very good pain control throughout the study and both formulations were well tolerated. There were no significant differences between MSC and MSS in pain scores or side effects. Under the conditions of this study there was no clinically significant difference in bioavailability between MSC and oral MSS. When given on a 12-hourly basis in individually titrated doses, the MSC provided therapeutic plasma morphine concentrations throughout the dosing interval.

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IN 1965, Houde and colleagues[1] reported that oral morphine had approximately one sixth the potency of intramuscular morphine. Later, Brunk and Delle[2] noted that, although oral morphine is well absorbed from the gastrointestinal tract, it is so rapidly metabolized in the intestinal mucosa and liver that only a fraction of the dose reaches the systemic circulation. These observations led to the incorrect conclusion, particularly in North America, that morphine is not an effective analgesic when given orally. However, studies by Saunders[3] and Twycross[4] in the United Kingdom and, later, by Melzack *et al.*[5,6] in Canada demonstrated that oral morphine given in regularly scheduled individually titrated doses is highly effective in controlling pain in a large majority of cancer patients. These apparently conflicting views have now

largely been resolved by our understanding (1) that the reduced oral bioavailability of morphine requires the administration of larger oral morphine doses to achieve the same effect as parenterally administered doses,[7,8] and (2) that, with repeated administration to patients with cancer pain, the parenteral/oral potency ratio of morphine is 1:2 or 1:3 rather than 1:6.[9]

In recent years, oral morphine has become recognized as a mainstay in the treatment of severe cancer pain.[10-12] Because the goal of analgesic therapy is to anticipate and prevent pain, not to treat it only as it reappears, each dose of oral morphine must be given before the effect of the previous dose has subsided. Because morphine has a short elimination half-life (2 to 3 hours), it must be administered every 4 hours if an optimal degree of efficacy and freedom from side effects are to be maintained. Unfortunately, a 4-hourly regimen is inconvenient for patients because it requires dosing during the night. Moreover, compliance is known to decrease as the required frequency of dosing increases,[13] and noncompliance adds to the risk of suboptimal pain control.

To overcome the difficulties associated with a 4-hour dosing regimen, controlled-release morphine sulfate tablets (MS Contin [MSC], Purdue Frederick, Inc., Toronto, Ontario, Canada) have been formulated using the Contin release system, which has been used successfully with a wide range of drugs.[14] The system consists of a matrix of aliphatic alcohols and alkyl cellulose. The rate of release of active drug from the matrix depends on the drug's partition coefficient between the components of the matrix and the aqueous phase within the gastrointestinal tract. Contin formulations control the rate of release of active drug within the gastrointestinal tract, with the result that the drug is delivered to the body at a specific, planned rate. The potential advantages of controlled-release formulations include extended duration of action, more constant plasma concentrations and clinical effects, reduced dosing frequency, increased compliance, and fewer side effects.

With drugs other than morphine, most notably theophylline,[15] controlled-release formulations have been found to be more effective than conventional formulations and better accepted by patients. However, these formulations also have some potential disadvantages. The release of active drug may be incomplete, resulting in reduced bioavailability, or the drug may be released too rapidly, producing toxic plasma concentrations. Also, because more drug is contained in controlled-release formulations, tablet size may increase, which, in turn, may lead to difficulty in swallowing.

MS Contin tablets have been in clinical use for several years, and studies have demonstrated excellent analgesic efficacy and a 12-hour duration of action in most patients.[16,17] However, only limited pharmacokinetic data are available, and no controlled pharmacokinetic study has been conducted in cancer patients. This study was undertaken to compare the pharmacokinetics and clinical efficacy of MSC tablets with those of oral morphine solution in patients with cancer pain.

Materials and Methods

Patients

Adult patients with cancer-related pain requiring oral opioid therapy participated in the study. All were mentally and physically competent to provide consent, answer questions, and comply with the therapeutic protocol, and all had serum creatinine levels of <130 μmol/l and serum bilirubin levels of <26 μmol/l. Patients with hepatic or renal impairment were excluded from the study, as were patients with severe nausea and/or vomiting or uncontrolled pain requiring frequent parenteral morphine and patients who were scheduled to receive a course of chemotherapy or radiotherapy in the 7 days before or at any time during the trial.

Patients provided written informed consent before participation. The study was approved by the Research and Ethics Committees of the Royal Victoria Hospital, Montréal, the Montreal General Hospital, the Ottawa General Hospital, and the Bureau of Human Prescription Drugs, Department of National Health and Welfare, Canada.

Test Medications

The test medications were MSC tablets in 30, 60, and 100 mg strengths and oral morphine sulfate solution (MSS) in 1 and 5 mg/ml concentrations. The MSS used at the Royal Victoria Hospital was prepared by the hospital's Department of Pharmacy and that used at the other centers was obtained commercially (Statex Pharmascience, Inc., Montréal). The MSC was administered every 12 hours, except to patients who required 90 mg/day. These patients received MSC 30 mg every 8 hours because 90 mg could not be given in two equally divided 12-hour doses with the tablet strengths available at the time of the study. The MSS was administered every 4 hours to all patients. Each patient's daily morphine dose was the same during both the MSC and MSS treatment periods. For example, a patient receiving 20 mg of morphine sulfate solution every 4 hours during MSS administration received 60 mg of morphine every 12 hours during MSC. Breakthrough pain was controlled by the use of separate, open-label doses of MSS. The date, time, and amount of MSS used for breakthrough pain was recorded.

Concomitant Medications

No opioids other than the test medications and the open-label MSS for breakthrough pain were given during

the trial. Nonopioid analgesics and other medications (*e.g.*, laxatives) that had been taken routinely by the patients before the trial were continued at stable doses during the trial.

Antiemetics, including prochlorperazine (10 mg three times daily), metoclopramide (10 mg three times daily), haloperidol (1–2 mg twice daily), and cyclizine (50 mg three times daily), were prescribed, as necessary, during the trial.

Study Design

The study was a double-blind, randomized, two-phase crossover comparison of the steady-state pharmacokinetics and analgesic efficacy of MSC and MSS. Each phase was at least 5 days long, and the order in which the patients received MSC and MSS was determined by a randomly generated allocation sequence. Blindness was maintained using the double-dummy technique, *i.e.*, each day patients received both tablet (every 12 hours or every 8 hours) and solution (every 4 hours) formulations, one active and the other a placebo.

Procedure

Initial doses: Patients who had been receiving oral morphine began taking test medication at the total daily morphine dose they had been taking before the trial. Patients who had not been receiving morphine before the trial started with a daily morphine dose calculated from a standard analgesic equivalency chart.[11]

Phase 1: Patients received the test medications at a constant daily dose for a minimum of 5 days to ensure that steady state had been reached. On the pharmacokinetic assessment day, a peripheral intravenous minicatheter was inserted just before the morning dose, and a blood sample was collected for morphine analysis. Patients then received their morning dose, and blood samples were collected every 30 minutes for the next 12 hours. Patients received their scheduled doses of MSS 4 and 8 hours after the morning dose, and, if they were receiving MSC on an 8-hourly schedule, they received their scheduled MSC dose.

Pain intensity was measured each day in the morning, at noon, at dinner time, and at bedtime using the present pain intensity (PPI) scale of the McGill pain questionnaire.[18] Side effects were recorded once daily, and their severity was rated using a four-point scale (0, none; 1, mild; 2, moderate; 3, severe). All extra doses of MSS used for breakthrough pain were also recorded. To avoid confounding the results of the pharmacokinetic comparison, a minimum of 24 hours elapsed between any use of extra morphine for breakthrough pain and blood sampling for pharmacokinetic assessment.

Phase 2: Patients crossed over to the other test medication on the day after the Phase 1 pharmacokinetic assessment. There was no washout period between the phases, and the daily morphine dose taken during Phase 1 was continued throughout Phase 2. Thus, with the exception of any extra morphine used for breakthrough pain, each patient's total daily morphine dose was the same during the MSC and MSS phases. Patients received the Phase 2 medication for at least 5 days, and the pharmacokinetic assessment was the same as in Phase 1.

Plasma Morphine Analysis

Plasma morphine concentrations were determined using a high-performance liquid chromatography technique.[19] Successful analyses were performed in 98% of the samples. In the remaining 2%, analysis could not be performed due to failure to obtain sufficient plasma or breakage of tubes in transport. Missing values were estimated by interpolation from neighboring concentrations.

Statistical Analysis

Model independent pharmacokinetic parameters, maximum plasma morphine concentration (C_{max}), minimum plasma morphine concentration (C_{min}), and time after administration at which the maximum plasma morphine concentration occurred (T_{max}) were determined for each patient directly from the raw data. The area under the curve (AUC) during MSC and MSS administration was calculated for each patient using the trapezoidal rule. For patients who received MSC every 12 hours, the AUC was calculated from zero to 12 hours postdose, *i.e.*, one 12-hour MSC interval and three 4-hour MSS dose intervals. For patients who received MSC every 8 hours, the AUC was calculated from 0 to 8 hours postdose, *i.e.*, one 8-hour MSC interval and two 4-hour MSS intervals. Pharmacokinetic parameters were compared using Student's *t* test.

Analysis of variance for repeated measures was used to compare the mean plasma morphine concentrations during MSC and MSS. Morphine concentrations at each time of sampling were compared by *t* tests. Because of the large number of comparisons (25 over the 12-hour sampling period), a nominal significance level of 0.002 was used to give an overall alpha error rate of approximately 0.05 ($25 \times 0.002 = 0.05$). In this context, an overall error rate of 0.05 means that the probability of erroneously declaring a significant difference between one or more pairs of means over the whole set of 25 comparisons is not greater than 0.05.

Wilcoxon's sign rank test was used to determine the significance of differences between the two medications in pain and side effect scores.

Linear regression analysis was performed to determine the relationship between plasma morphine concentrations and daily morphine dose (mg/kg) using a method that required the regression line to pass through the origin.

TABLE 1. Patient Characteristics

Sex (no. of patients)	
Male	13
Female	10
Age (yr)*	58 ± 12
Weight (kg)*	58 ± 16
Prestudy analgesics (no. of patients)	
Morphine	19
Indomethacin + aspirin	2
Anileridine	2
Primary site of malignancy or type (no. of patients)	
Lung	7
Colon	3
Urinary bladder	3
Breast	2
Pancreas	1
Prostate	1
Stomach	1
Mediastinal germ cell tumor	1
Multiple myeloma	1
Osteosarcoma	1
Squamous cell carcinoma	1
Unknown primary	1

*(Mean ± SD).

Results

Twenty-eight patients enrolled in the study. Two patients were removed from the study during Phase 1, both due to increasing somnolence and disorientation necessitating withdrawal of morphine. At the time of discontinuation, one patient was receiving MSC, and the other MSS. The trials of two other patients were discontinued on the first pharmacokinetic assessment day because of difficulty in obtaining blood samples. The data from one patient were excluded from analysis because he received an extra dose of morphine on one of the pharmacokinetic sampling days. The characteristics of the 23 patients included in the analysis are shown in Table 1. Randomization resulted in 11 patients receiving MSC in Phase 1 and MSS in Phase 2. The other 12 patients received the medications in the opposite sequence. There were no significant differences between the two groups in mean age, weight, or daily morphine dose. The results are expressed as mean ± standard deviation.

Overall Pharmacokinetic Data

The daily morphine doses (mean, 163.5 mg) and pharmacokinetic values calculated for each patient during the two regimens are listed in Table 2. There was no significant difference in bioavailability between MSC and MSS. The mean AUCs for MSC and MSS were 394.4 and 353.1 ng/ml/hour, respectively. The 95% confidence interval for the bioavailability of MSC relative to MSS was 98% to 125%.

Three patients (Patients 3, 13, and 20) had marked differences in plasma morphine concentrations and AUCs between the two phases. For Patients 3 and 20, the plasma concentrations-*versus*-time profiles for both drugs had the expected configuration, but concentrations during one phase were approximately twice those of the other. During MSC treatment, Patient 13 showed a steady decline in concentrations beginning 1 hour after administration and continuing to the end of the sampling period, suggesting that this patient may not have received the test medication or that the dose was administered considerably earlier than scheduled. However, a thorough review of the records of these three patients revealed no discrepancies, and their data therefore were included in the analysis.

The mean C_{max} during MSC administration (62.4 ng/ml) was significantly ($P < 0.05$) greater than that during treatment with MSS (54.1 ng/ml). There was no significant difference in mean C_{min} between the two drugs (16.1 and 16.5 ng/ml for MSC and MSS, respectively). The C_{max}/C_{min} is a measure of the amplitude of the fluctuation in plasma morphine concentrations. The C_{max}/C_{min} during MSC was 4.6 ± 1.8. During MSS it was 3.9 ± 1.6 ($P > 0.20$). During MSS administration, fluctuations of this amplitude occurred every 4 hours, whereas they occurred every 12 or 8 hours while the patients were taking MSC.

Linear regression analysis revealed a very close correlation between dose and morphine concentrations during both MSC ($r = 0.94$) and MSS ($r = 0.96$). Figure 1 shows the fitted regression line and each patient's mean plasma morphine concentration during both phases as a function of daily morphine dose. The 95% confidence limits for the slope of the line are 10.7 and 13.1.

As would be anticipated in a comparison of controlled-release and immediate-release formulations, there was a very highly significant ($P < 0.001$) difference between the mean T_{max} values obtained with the two preparations (3.4 and 1.2 hours with MSC and MSS, respectively).

MS Contin (Every 12 Hours) Group

The mean MSC and MSS plasma morphine concentration-*versus*-time profiles of the 18 patients who received MSC on a 12-hourly schedule are compared in Figure 2. The mean concentration during treatment with MSC was significantly greater than that during MSS at 3.5 and 4.0 hours. At no time did MSS produce a significantly higher mean concentration than MSC, although the difference at 9.0 hours approached significance (corrected $P = 0.10$).

Inspection of Figure 2 reveals that the highest mean concentration during MSC occurred 4.5 hours after administration. The mean concentration at 4.5 hours was significantly higher than that at 0 hour and those from 7.5 to 12 hours. Thus, by virtue of the nonsignificant differences, the period from 0.5 to 7.0 hours must be considered the plateau period. Each 4-hourly dose of MSS produced a C_{max} at 1.0 hour, and this concentration was

TABLE 2. Individual Steady-State Pharmacokinetic Parameter Values in 23 Cancer Patients* During MS Contin and Oral Morphine Sulfate Solution Treatments

Patient	Morphine dose (mg/day)	C_{max} (ng/ml)		C_{min} (ng/ml)		T_{max} (hr)		AUC (ng/ml/hr)†	
		MSC	MSS	MSC	MSS	MSC	MSS	MSC	MSS
1	180	51.5	65.9	13.0	15.2	1.0	1.5	357.5	404.2
2	180	68.7	71.8	13.4	16.1	4.0	1.5	482.0	439.0
3	60	33.8	54.5	8.5	9.6	9.0	1.3	165.2	309.0
4	180	126.6	87.8	46.8	45.3	4.5	1.7	877.5	809.0
5	120	24.4	32.6	5.0	9.4	3.5	0.8	178.5	203.0
6	60	56.5	42.7	7.1	10.2	1.5	2.2	229.8	227.7
7	400	197.3	143.1	69.3	56.8	8.0	1.7	1514.7	1128.0
8	120	34.4	25.1	7.2	8.9	3.0	0.8	229.7	184.7
9	120	43.6	31.6	8.3	3.8	2.5	1.3	261.7	166.0
10	60	36.0	26.0	8.5	4.3	2.0	1.2	270.7	168.7
11	60	62.6	24.0	7.3	9.6	1.5	1.2	219.0	187.5
12	120	74.9	53.0	18.1	9.3	2.0	1.0	482.5	332.5
13	120	34.3	46.1	0	5.3	1.0	1.8	92.2	227.2
14	180	75.4	74.6	14.1	20.1	4.5	1.2	548.7	435.2
15	360	52.2	51.4	16.8	24.6	5.0	0.8	345.0	460.2
16	180	65.7	65.7	7.5	18.7	3.0	0.8	361.4	434.5
17	600	114.5	100.9	42.0	41.4	2.5	1.2	905.7	760.0
18	210	70.3	61.8	13.0	20.8	5.5	0.7	463.2	445.7
19	90	30.2	35.0	8.7	11.3	3.0	0.5	172.2	180.2
20	90	40.4	36.1	12.1	5.3	1.5	0.8	230.7	116.2
21	90	48.7	29.2	13.2	10.2	2.5	0.3	215.0	153.7
22	90	39.5	44.6	14.3	12.8	1.9	1.2	234.2	177.0
23	90	53.0	39.9	15.6	11.7	5.0	1.2	234.5	172.0
Mean	163.5	62.4	54.1	16.1	16.5	3.4	1.2	394.4	353.1
SD	129.3	38.7	28.3	15.7	13.7	2.1	0.4	321.0	251.2
Significance of difference		$P < 0.05$		NS		$P < 0.001$		NS	

MSC: MS Contin; MSS: morphine sulfate solution; C_{max}: maximum plasma morphine concentration; C_{min}: minimum plasma morphine concentration; AUC: area under the curve; T_{max}: time after administration at which C_{max} occurred; NS: not significant.

* Patients 1 through 18 received MSC every 12 hr in equally divided doses; Patients 19 through 23 received MSC 30 mg every 8 hr; MSS was given every 4 hr to all patients.

† Calculated from 0 to 12 hr postdose for Patients 1 through 18 and from 0 to 8 hr postdose for patients 19 through 23.

usually significantly greater than the concentrations at 0 hour and between 2.5 and 4.0 hours. There were some differences between the three MSS doses. The dose interval from 0 to 4 hours had a substantially longer period of nonsignificant differences than did that from 8 to 12 hours.

There were also differences in the AUCs for the three consecutive MSS dose intervals. The mean AUCs for the first, second, and third intervals were 138.5 ± 82.8, 144.2 ± 93.1, and 124.1 ± 88.0 ng/ml/hour, respectively. When tested by analysis of variance, the AUC for the third interval (8–12 hours) was found to be significantly ($P < 0.05$) less than that of the first and second.

The values for the pharmacokinetic parameters calculated for the 18 patients in the 12-hourly MSC group are given in Table 3.

MS Contin (Every 8 Hours) Group

The mean MSC and MSS plasma morphine concentration-*versus*-time profiles of the five patients who received MSC every 8 hours are compared in Figure 3. Although the mean concentrations were generally greater during MSC than during MSS, at no time point did the difference between the two reach statistical significance. The pharmacokinetic parameter values for these patients are given in Table 4.

Pain Scores, Side Effect Ratings, and Use of Extra Morphine

All 23 patients generally experienced very good pain control during both phases of the study, and clinically there was no overt difference in pain severity between the two phases for any patient. Because five patients failed to fully complete their daily diaries, data from only 18 patients were used in the detailed comparison of the PPI pain scores and side effect ratings of the two treatments. The PPI pain score during MSC treatment was 0.55 ± 0.58, and during MSS it was 0.57 ± 0.63 ($P = 0.85$).

Both medications were very well tolerated throughout the study, with only three patients reporting mild nausea during MSC and three different patients reporting mild

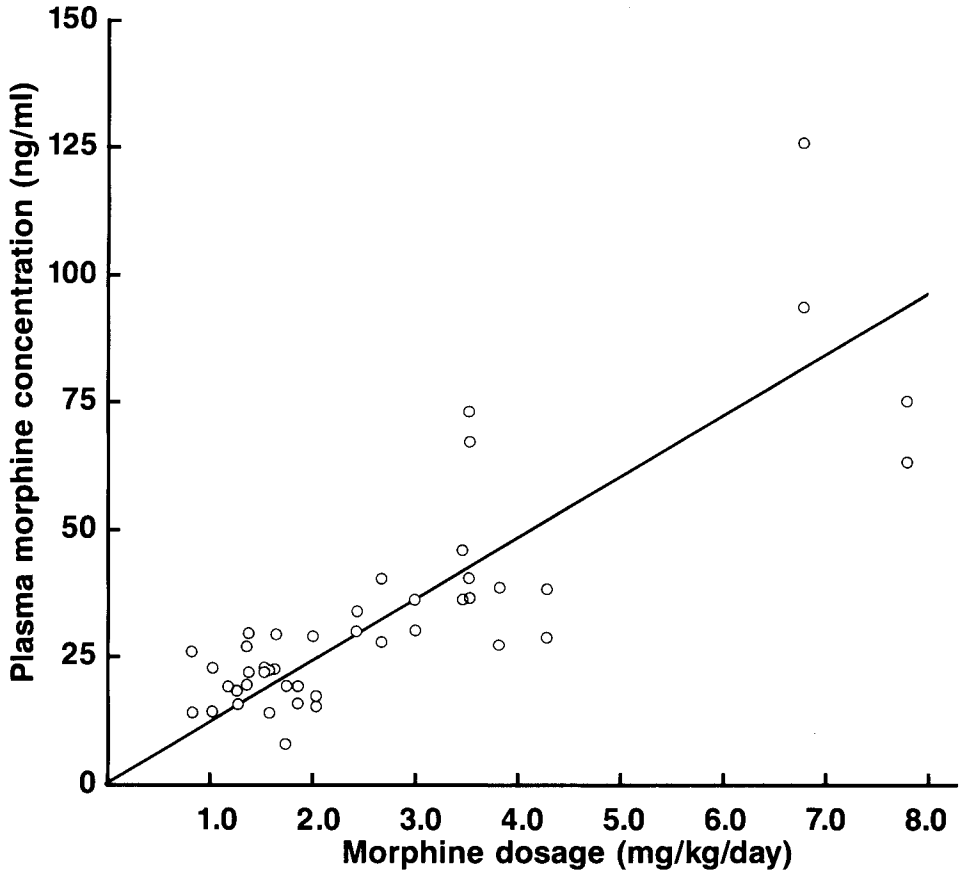

FIG. 1. Mean plasma morphine concentration *versus* daily morphine dose in 23 cancer patients during MS Contin and oral morphine solution administration. Scattergram and least-squares linear regression line through the origin (Y = 11.9X; r = 0.94).

nausea with MSS. The severity scores for nausea during MSC and MSS were 0.06 ± 0.13 and 0.07 ± 0.17, respectively. Three patients also reported mild dizziness during the two phases, with no significant difference in either incidence or mean severity between the two drugs.

The use of extra morphine to control breakthrough pain

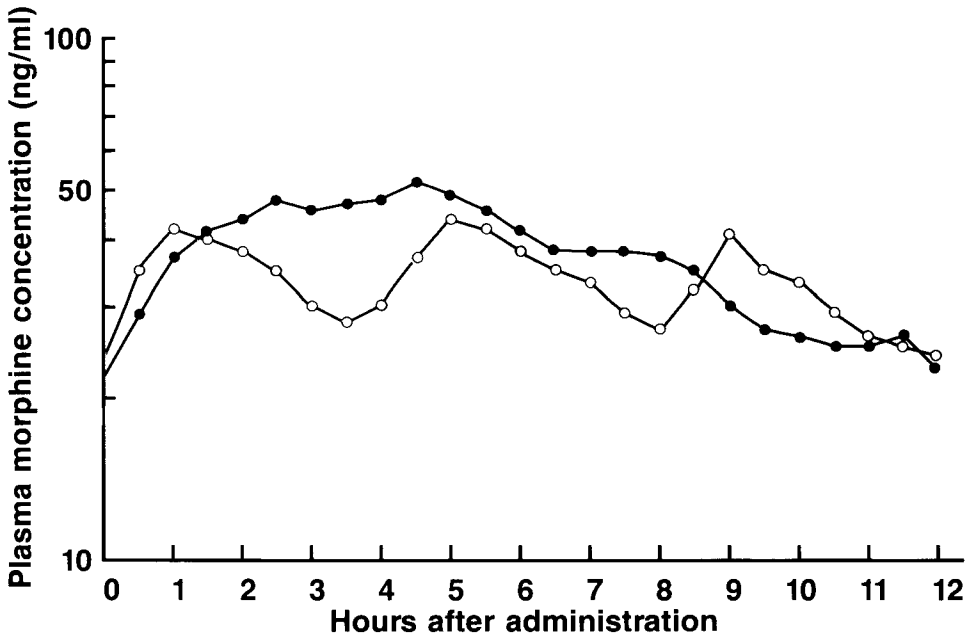

FIG. 2. Mean steady-state plasma morphine concentration as a function of time after administration in 18 cancer patients after MS Contin every 12 hours (●) and oral morphine solution every 4 hours (○). The mean total daily morphine dose was 183.9 ± 140.0 mg.

was minimal. While taking MSC, three patients each required one extra dose. During MSS administration, two patients required one dose and a third required two doses. The amount of extra morphine used for breakthrough pain represented less than 1% of the morphine administered during the study.

Discussion

MS Contin has been marketed for several years, but only limited information on the pharmacokinetics of this preparation has been available, particularly information on its pharmacokinetics in cancer patients. Difficulties with various analytical techniques for measuring morphine concentrations have been a principal obstacle in obtaining such data, and it is now known that the assays used in earlier patient studies[20–22] were neither sensitive nor specific enough to produce unequivocal results. The high-performance liquid chromatography method used in this study is highly specific and allows the measurement of concentrations as low as 1.0 ng/ml with an average relative precision of 5.0% over a range of 1 to 200 ng/ml. It thus overcomes the problems associated with earlier techniques.[19]

The steady-state plasma concentration-*versus*-time profile obtained in cancer patients taking MSC every 12 hours (Fig. 2) demonstrates that the prolonged release of morphine from the tablets reduces both the rate of absorption and the rate of decline of plasma morphine concentration. As a result, doses of MSC that are three times those of MSS result in approximately equivalent maximum and minimum plasma morphine concentrations and a similar amplitude of fluctuation. Inasmuch as clinical experience has demonstrated that morphine solution most often has optimal efficacy when given every 4 hours,[11,12,23] our pharmacokinetic findings indicate that a 12-hourly regimen of MSC should similarly be optimal for most patients. The reduction in the frequency with which plasma concentrations fluctuate during MSC may also be clinically important, although this was not apparent in the current study.

These study patients received very good pain control throughout both phases of the study. In several other controlled clinical comparisons, 12-hourly MSC has been shown to control cancer pain as effectively as a 4-hourly morphine solution.[24–28] Although plasma morphine concentrations were declining at the end of the dose interval, at no time did they fall significantly below the corresponding concentrations obtained with MSS. A recent carefully controlled efficacy study has also documented that there is no loss of analgesic efficacy over the last few hours of the MSC dose interval.[17]

TABLE 3. Steady-State Pharmacokinetic Parameter Values (Mean ± SD) Obtained in 18 Cancer Patients Receiving MS Contin Every 12 Hours

	MSC	MSS	Significance of difference
C_{max} (ng/ml)	67.9 ± 42.1	58.8 ± 30.3	NS
C_{min} (ng/ml)	17.0 ± 17.7	18.3 ± 15.0	NS
T_{max} (hr)	3.6 ± 2.3	1.3 ± 0.4	$P < 0.001$
AUC (ng/ml/hr)	443.6 ± 348.4	406.8 ± 259.7	NS

MSC: MS Contin; MSS: morphine sulfate solution; NS: not significant; C_{max}: maximum plasma morphine concentration; C_{min}: minimum plasma morphine concentration; T_{max}: time after administration at which C_{max} occurred; AUC: area under the curve.

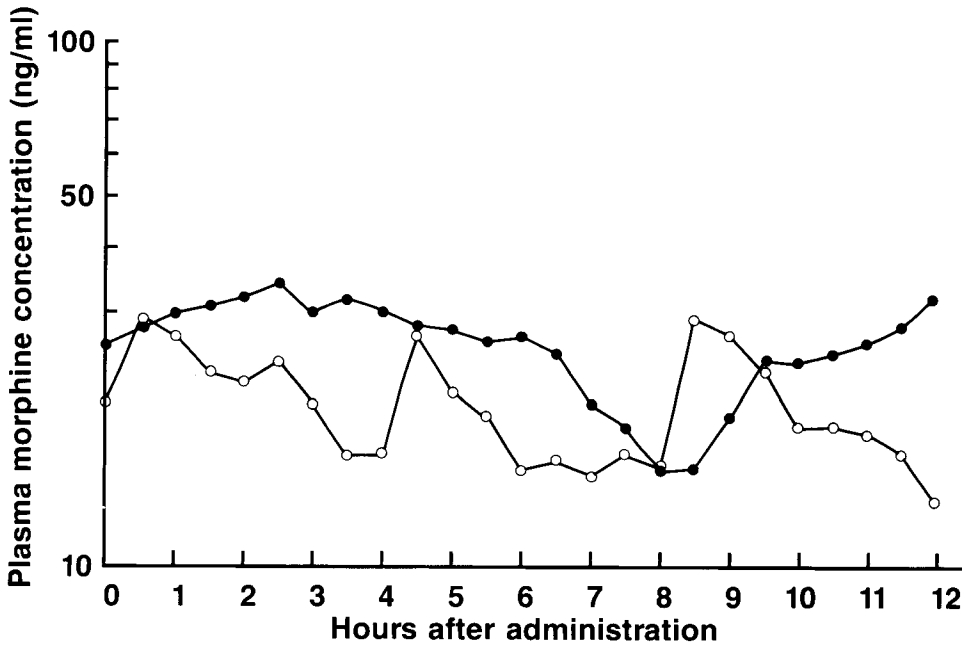

FIG. 3. Mean steady-state plasma morphine concentration as a function of time after administration in five cancer patients during the administration of MS Contin every 8 hours (●) and oral morphine solution every 4 hours (○). Each patient's total daily morphine dose was 90 mg.

TABLE 4. Steady-State Pharmacokinetic Parameter Values (Mean ± SD) Obtained in Five Cancer Patients Receiving MS Contin Every 8 Hours

	MSC	MSS	Significance of difference
C_{max} (ng/ml)	42.4 ± 8.9	37.0 ± 5.7	NS
C_{min} (ng/ml)	12.8 ± 2.6	10.3 ± 2.9	NS
T_{max} (hr)	2.8 ± 1.4	0.8 ± 0.4	$P < 0.02$
AUC (ng/ml/hr)	217.3 ± 26.5	159.8 ± 26.5	$P < 0.05$

MSC: MS Contin; MSS: morphine sulfate solution; NS: not significant; C_{max}: maximum plasma morphine concentration; C_{min}: minimum plasma morphine concentration; T_{max}: time after administration at which C_{max} occurred; AUC: area under the curve.

MSC was administered every 8 hours to five patients, all of whom required daily morphine doses of 90 mg, which could not be administered in two equally divided doses with the tablet strengths available at the time of the study. Since then, a 15-mg tablet has been introduced in Canada, which allows the administration of doses of 45 mg every 12 hours. The pharmacokinetic results in the 8-hour MSC group suggest that this regimen produces a greater AUC than MSS, but there were no clinically significant differences between the formulations. Because MSC provides effective plasma morphine concentrations for 12 hours, there is little rationale for more frequent dosing.

Overall, the mean AUC (bioavailability) of MSC was 12% greater than that of MSS, but the difference was not statistically significant ($P = 0.09$). Given that the 95% confidence interval for the bioavailability of MSC relative to MSS was 98% to 125%, it is unlikely that there is a clinically significant difference in bioavailability between the two formulations. This conclusion is supported by a recent steady-state comparison of MSC and MSS conducted in healthy volunteers.[29] The finding that the AUC differed significantly among the individual MSS dosing intervals may reflect a diurnal variation in morphine kinetics, or the patients' food intake before the third MSS dose may have inhibited morphine absorption. A significant food effect appears unlikely, however, since, in a separate study, food showed no effect on morphine kinetics after MSC administration.[30] The variation in AUC seen after sequential doses of MSS has implications for the design of comparative bioavailability studies, since it is apparent that the formulations to be compared must be given in equal doses over identical periods of observation (as was the case in the current study). An assumption that the AUC of any MSS dosing interval is representative of the AUC of all dosing intervals could result in an inaccurate estimate of the 0-hour to 12-hour AUC.

In some patients we found a sustained plateau in the MSC concentration-*versus*-time curve. For example, in one patient plasma concentrations of 40.4, 39.4, 39.5, and 38.0 ng/ml were found 1.0, 1.5, 2.0, and 4.0 hours after administration, respectively. In another, concentrations of 196.0, 197.3, and 185.5 were seen at 4.5, 8.0, and 8.5 hours, respectively. In such cases, determination of C_{max} and T_{max} directly from the data requires an arbitrary decision, and these traditional parameters alone are not a particularly good representation of the plasma concentration-*versus*-time profile of a controlled-release preparation. Novel parameters designed to reflect the duration of relatively stable plasma concentrations may be more useful.[31] Plateau concentration, duration of plateau, and curve width at 50% of C_{max} have been suggested, but it remains to be determined which are the most appropriate.

Conclusion

Our study demonstrates that, in patients with cancer-related pain, MSC provides effective plasma morphine concentrations throughout a 12-hour dosing interval with minimal side effects. The bioavailability of MSC given every 12 hours was not significantly different from that of MSS given every 4 hours, which supports the use of a daily milligram equivalency when transferring patients from MSS to MSC. As with any change of medication, individual patients may require later dose adjustments. Because MSC is effective throughout a 12-hour dosing interval, there is little rationale for more frequent administration. The small tablet size and 12-hour duration of analgesia of MSC provide convenience for patients and caregivers, and it thus is an important alternative to 4-hourly doses of MSS for the management of cancer-related pain.

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